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EFFECTS OF METHAMPHETAMINE ON VIGILANCE AND TRACKING DURING EXTENDED WAKEFULNESS

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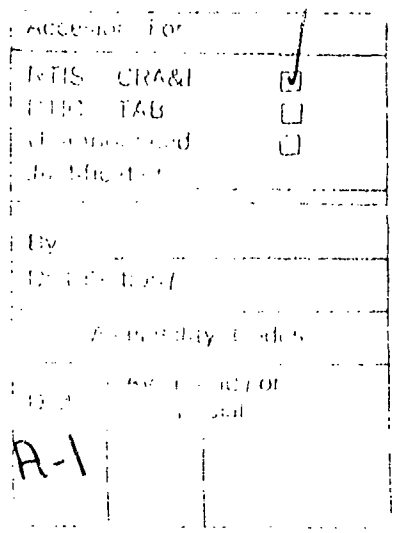
ABSTRACT

We examined the effects of a 10 mg/70 kg oral dose of *d*-methamphetamine HCl on high-event-rate vigilance and tracking performance in a 13.5-h sustained-performance session during a night of sleep loss. At 0116 hours, seven subjects were administered *d*-methamphetamine, double-blind. The remaining six subjects were given a placebo. Values of sensitivity (d') in the vigilance task declined markedly during the night in the placebo group. The methamphetamine treatment reversed an initial decline in d' within approximately 2 h of administration. The methamphetamine treatment also reversed increases in nonresponses (lapses) within approximately 2 h of administration. Tracking performance also declined markedly during the night in the placebo group. The methamphetamine treatment reversed the decline in tracking performance. An analysis of fast guesses in the vigilance experiment disclosed no evidence to suggest that methamphetamine tended to increase impulsive responding. In fact, the methamphetamine treatment was associated with a small (and nonsignificant) reduction in fast guesses. The overall pattern of the results suggests that methamphetamine at 10 mg/70 kg produces genuine increases in efficiency that effectively counteract the effects of continuous work during a night of sleep loss.



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INTRODUCTION

Changes in technology, political environment, and doctrine suggest that future conflicts may emphasize periods of high-intensity sustained operations (SUSOPs). The term 'sustained operation' is defined as continuous combat with no opportunity to sleep (U.S. Army, 1983). The related term, 'continuous operation,' (CONOP) is defined as continuous combat with occasional opportunities for sleep (U.S. Army, 1983). The term, 'sustained operation,' has occasionally been generalized to refer to any unusually long bout of work performed nonstop for as long as necessary or possible (e.g., Krueger, 1989). Examples of activities that meet this definition include lengthy medical-emergency procedures, some types of military training, long search-and-rescue operations, disaster-relief missions, accident evacuations, and forest-fire fights (Krueger, 1989). The Navy's newly defined regional, littoral focus requires maintaining an ability to deploy expeditionary forces rapidly and an ability to sustain distant operations for long periods of time (O'Keefe, Kelso & Mundy, 1992). Fiscal reality suggests that these needs will be addressed with smaller forces. Therefore, rates with which personnel can be deployed, speeds with which hostilities can be escalated, and levels of force that can be sustained will increasingly depend on the degree to which individuals can be protected from fatigue and circadian effects due to long hours of work. The implications of fatigue for mission effectiveness and safety are well understood by operational commands. Some 26% of major nonejection accidents in naval combat (ejection-seat) aircraft and 24% of associated deaths and presumed deaths may be attributable to failures of attention, and 15% of such accidents and 13% of the associated deaths and presumed deaths may be attributable to sleep deprivation, fatigue, and/or circadian phenomena.[1] Concerns about these dangers have led several operational commands to voice strong support for the development of guidelines for using pharmacological agents to protect aircrew from the worst effects of fatigue. For example:

> The Naval Strike Warfare Center recognizes aircrew fatigue as adversely affecting both operational effectiveness and safety-of-flight....Adoption of protocols by BUMED for use of anti-fatigue medication is strongly recommended [Naval Strike Warfare Center, NAS, Fallon, NV, Ltr 6410, Ser 40/675-91 of 31 Oct 91].
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> Aircrew fatigue during extended contingency operations has been recognized as a factor which can limit the operational effectiveness of aviation units and jeopardize aircrew safety. The Naval Fighter Weapons School supports the development of a protocol for the use of stimulants and sedatives to enhance aircrew performance during prolonged periods of increased tasking due to operational necessity [Navy Fighter Weapons School, Naval Air Station, Miramar, San Diego, CA, Ltr 6410 Ser 00/102 of 3 Feb 92].
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> Operational contingencies requiring sustained around the clock flights with high aircrew tasking may sufficiently degrade performance to the point of adversely affecting safety of flight and mission accomplishment. Marine Aviation Weapons and Tactics Squadron One acknowledges that low dose stimulant and sedative medication, taken under close medical supervision, with the commander's approval, can effectively counter fatigue in certain situations [Marine Aviation Weapons and Tactics Squadron 1, MCAS, Yuma, AZ, Ltr 6000, 5, 3 Sep 92].

The present study was undertaken as part of a program intended to produce quantitative data comparing the relative efficacies of several pharmaceutical and nonpharmaceutical countermeasures in reducing the effects SUSOPs. In the study reported here, we examined the effects of a 10 mg/70 kg oral dose of *d*-methamphetamine HCl on vigilance and psychomotor tracking deficits caused by extended wakefulness. We are interested in quantifying the effectiveness of putative fatigue countermeasures, such as methamphetamine, in a SUSOPs

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[1]These statistics are from an analysis of investigators' judgements of factors contributing to major accidents in U.S. Navy ejection seat aircraft. Data were obtained from the U.S. Navy Aircrew Mishap Experiences Data Base, Naval Air Systems Command, Washington Navy Yard, Washington, DC. (R. Stanny, unpublished analysis, 1992).

scenario with a time course resembling those frequently encountered in Navy and Marine sustained tactical air operations. These conditions differ somewhat from those encountered in ground-troop sustained operations. A significant difference is that ground warfare may involve periods of sleep deprivation in excess of 48 h. For example, classical Soviet doctrine for European war called for ground troops to fight continuously for 2-4 days before being replaced by fresh troops (Belenky et al., 1986). Although imaginable, scenarios in which naval aviators are tasked to fly after several nights of sleep deprivation seem highly unlikely.

The performance scenario examined in the present study required subjects to work continuously through a night of sleep deprivation following an ordinary day's activities. Similar patterns of continuous work and sleep deprivation occur in sustained air operations during rapid deployments, extended patrol missions, and long-range attack missions. Civilian examples include lengthy medical-emergency procedures, long search-and-rescue operations, disaster-relief missions, accident evacuations, and forest-fire fights (Krueger, 1989). Our experimental paradigm, therefore, differs from designs that have frequently been used to study ground-troop performance maintenance (for reviews, see Belenky et al., 1986; Krueger, 1989). Ground-troop designs have typically involved very long periods of sleep deprivation, often in the range of 48-72 h. Consequently, to avoid floor effects, the tasks used to measure performance in those designs must be easy enough that individuals can perform them adequately after several days of sleep deprivation. Easy tasks, however, tend to have low performance ceilings, which can make them unsuitable for measuring changes in performance during the first day or two of sleep deprivation. For example, the Walter Reed Performance Assessment Battery (and those test batteries derived from it) is insensitive to fatigue effects smaller than those produced by about 2 days of sleep deprivation (G. L. Belenky, Walter Reed Army Institute of Research, Personal Communication, February, 1993; Newhouse et al., 1992).[2]

EFFECTS OF SUSTAINED OPERATIONS

Effects of extended wakefulness include irritability, forgetfulness, mental lapses, a growing aversion to further effort and, sometimes, hallucinations (Bartlett, 1943; Bills, 1931; Folkard, Condon, & Herbert, 1984; Hockey, 1986; Johnson & Naitoh, 1974; Patrick & Gilbert, 1896; Warren & Clark, 1937; Williams, Gieseking, & Lubin, 1966; Williams, Lubin, & Goodnow, 1959). These are presumably due to interactions among the effects of fatigue, sleep-loss, and circadian phenomena (Hockey, 1986; Krueger, 1989).

Fatigue effects are perhaps most appropriately defined as performance deficits caused by repeatedly carrying out the same or similar activities (Eisenberger, 1992; Mast & Heimstra, 1964; Solomon, 1948). However, the term is frequently used in ordinary language to refer to the subjective effects of sleep deprivation and circadian disruption. Feelings of both stress and boredom are frequent consequences of repetitive mental work and might be considered to be among the effects of mental fatigue (e.g., Holding, 1983).

Sleep deprivation effects, according to an historically important hypothesis, are dominated by periodic bouts of lapses, distractions, or microsleeps that intrude on otherwise normal performance (Broadbent, 1963; Williams, Lubin, & Goodnow, 1959). As sleep deprivation continues, the individual's performance may continue on a reasonably acceptable level, broken by lapses of attention (Williams et al., 1959). Sleep-deprived subjects may carry out tasks with apparent accuracy but their periods of accuracy become briefer and more infrequent as sleep deprivation continues. Laboratory investigations of the effects of sleep deprivation during

[2]This should not necessarily be considered a flaw of the Walter Reed and similar test batteries. Although ceiling effects may render an easy test insensitive to change in mental capacity when capacity is high, floor effects may render a difficult test insensitive to change in capacity after a short period of sleep deprivation. Tests that are both reasonably brief (well under an hour in duration) and sensitive to change in capacity over the entire capacity range are difficult to construct.

continuous performance have demonstrated substantial declines in mood and performance after 18 h of continuous testing, and (usually) unacceptable performance after 42 h of sustained wakefulness (e.g., Babkoff, Genser, Sing, Thorne, & Hegge, 1985; Babkoff, Mikulincer, Caspy, Kempinski, & Sing, 1988; Horne, Anderson, & Wilkinson, 1983; Naitoh, Englund, & Ryman, 1987; Thorne, Genser, Sing, & Hegge, 1983; Williams, Lubin, & Goodnow, 1959; Wilkinson, 1964).

Circadian effects include rhythmic oscillations in protein synthesis, neurotransmitter availability, body temperature, and other biological processes. These, in turn, are associated with daily cycles in memory processes, vigilance, decision speed, and other psychological functions (Babkoff, Caspy, Mikulincer, & Sing, 1991; Babkoff et al., 1985, 1988; Deaton, Tobias, & Wilkinson, 1972; Folkard & Condon, 1987; Folkard, Condon, & Herbert, 1984; Folkard, Knauth, Monk, & Rutenfranz, 1976; Folkard & Monk, 1980; Folkard, Monk, Bradbury, & Rosenthal, 1977; Hockey & Colquhoun, 1972; Horne, Anderson, & Wilkinson, 1983; Idzikowski, 1984; Richardson & Rose, 1971; Rusak & Bina, 1990; Wilkinson, Edwards, & Haines, 1966; Ziegler, Lake, Wood, & Ebert, 1976). In recent years, a large body of information has accumulated showing time-of-day effects in performance. Some researchers, in fact, have suggested that the effects of circadian variation may have a greater impact on mood and performance than shortened hours of sleep (Johnson, 1979). Under normal conditions, circadian rhythms are entrained to approximately 24-h periods by Zeitgebers that serve as time cues for the oscillating system (Nicholson & Stone, 1982). On most tasks, performance rises during the day to a peak or plateau between 1200 and 2100 and falls to a minimum between 0300 and 0600 hours. A secondary trough in performance occurs just after noon. The "post-lunch dip" usually occurs whether or not lunch is eaten. The circadian rhythm in performance is similar to the body-temperature rhythm, except that the post-lunch dip in temperature may not occur (Nicholson & Stone, 1982). Otherwise, the association between temperature and performance is so strong that temperature is sometimes used as an implicit index of performance (Kleitman, 1967).

PERFORMANCE EFFECTS OF AMPHETAMINE-LIKE STIMULANTS

The consequences of sustained operations for fatigue may sometimes call for the use of central stimulants. In the following sections, we review some evidence on the performance effects of amphetamine-like stimulants and their mechanisms. The review focuses on the amphetamines because they have been most widely studied, the resulting data are most relevant to the study at hand, and because these drugs are the most effective pharmaceutical fatigue countermeasures available. The bulk of the experimental work on stimulants has been conducted with the amphetamines, particularly *d*-amphetamine. The amphetamines are generally accepted as effective against the effects of sleep deprivation on mood and performance. The effects of amphetamines on mood are unquestioned. However, despite the acceptance of amphetamines as stimulants, the data from controlled experiments do not uniformly indicate that amphetamines always improve performance.

A number of questions remain with regard to the performance effects of the amphetamines and similar drugs. Although the amphetamines improve mood, it is not clear that they necessarily improve cognition. First, some data suggest that amphetamines may impair memory. Second, other data suggest that the increased decision speed sometimes attributed to amphetamine may, in fact, reflect changes in response criteria (changes in the direction of overly confident, impulsive responding). If this is true, some of the evidence customarily cited as indicating that amphetamines improve performance may, in fact, indicate the opposite.[3] Third, the results of many studies of amphetamine effects are simply contradictory. These issues are discussed in the following paragraphs.

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[3]Many experimental protocols used in studies of amphetamine effects have confounded changes in performance efficiency with changes in response bias (Hockey, 1986).

Neural bases of amphetamine effects

The central nervous stimulant properties of amphetamines are believed to be at least partly due to their ability to enhance the release and reuptake of catecholamines (Kuczenski, 1983). It is well established that amphetamine administration influences the firing rates of noradrenergic and dopaminergic neurons (Bunney, Aghajanian, & Roth, 1973; Graham & Aghajanian, 1971). Different functions have been ascribed to brain norepinephrine (NE) and dopamine (DA) systems (reviewed by Clark, Geffen, & Geffen, 1987a,b; Oades, 1985). According to one widely discussed hypothesis, NE-carrying neurons modulate the signal-to-noise ratios of neural discharges at fairly early stages of sensory processing.[4] In contrast, DA mechanisms may operate later in processing, perhaps by facilitating switching among motor programs or modulating the strengths of associations between internal representations of stimuli and responses (Clark et al., 1987a,b; Oades, 1985).

Neurophysiological studies suggest that a major system of NE-carrying neurons is in some way associated with arousal processes. The cell bodies of these neurons are located in the locus coeruleus (LC); (Foote, Bloom, & Aston-Jones, 1983). Locus coeruleus is the sole source of norepinephrine terminals in rat neocortex and may also be the primary source of NE innervation to much of primate neocortex (Fallon & Laughlin, 1984; Foote, et al., 1983). Cortical NE systems have been implicated in a number of other processes, including memory consolidation (Zornetzer, Abraham, & Appleton, 1978), anxiety (Redmond & Huang, 1979), neuronal plasticity (Kasamatsu, Hakura, Johnson, Heggelund, Pettigrew, Nakai, Watabe, Kupperman, & Ary, 1984), and cerebral circulation control (Magistretti & Morrison, 1985). It is logically possible that more than one of these hypotheses is correct; indeed, Fallon and Laughlin (1984) have speculated that, given the widespread distribution of LC terminals and the variety of processes implicated, LC activity might subserve a global process that influences a wide variety of behaviors.

The responses of LC-NE neurons vary strongly with vigilance levels. These cells' lowest activity levels occur during slow wave and rapid eye movement sleep, whereas their highest activity levels occur during waking vigilance and orienting (Aston-Jones & Bloom, 1981; Aston-Jones, Segal, & Bloom, 1980; Foote, Aston-Jones, & Bloom, 1980). Foote et al. (1983) suggest that LC-NE neurons function to enhance the reliability and efficiency of feature extraction from sensory inputs. Consistent with this suggestion, iontophoretically applied NE and direct LC stimulation have been observed to reduce the spontaneous (background) discharge rates of cells in auditory, visual, and somatosensory cortex, thus effectively increasing the signal-to-noise ratios of the cells' stimulus-driven discharge patterns (Foote, Freedman, & Oliver, 1975; Kasamatsu & Heggelund, 1982, Livingstone & Hubel, 1981; Videen, Daw, & Rader, 1984; Waterhouse, Moises, & Woodward, 1980, 1981; Waterhouse & Woodward, 1980). If the cells whose signal-to-noise ratios are increased by NE actually mediate perception or discrimination, it is possible that amphetamine-related increases in NE availability could lead to improved information processing.

A contrasting hypothesis of early NE effects leads to the prediction that amphetamine administration might instead cause increases in response speeds accompanied by increases in errors. This hypothesis has been proposed by Posner and Peterson (1990), who argue that alertness fluctuations attributable to NE mechanisms affect response criteria without increasing the quality of perceptual information (see also Posner, 1978). According to this model, the response-biasing effects of NE-mediated arousal cause visual decisions made in alerted states to be more rapid and error-prone than decisions made in nonalerted states. Posner and Peterson suggest that one class of visual alerting effects is controlled by NE-bearing locus coeruleus projections to an

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[4]One way to quantify the signal-to-noise ratio of a neuron's stimulus-driven activity is to divide the change in the cell's discharge rate caused by turning on an external stimulus (i.e., its driven rate in spikes/s) by the cell's spontaneous discharge rate (its spike rate in the absence of the stimulus). Different calculations are sometimes used. However, the basic idea of quantifying the amount of stimulus information transmitted in a cell's firing pattern is usually the same.

attentional subsystem of the dorsal spatial-vision pathway. This system, in turn, can influence processing in the ventral, object-recognition pathway, perhaps indirectly via thalamic connections (see also Ungerleider & Mishkin, 1982). If Posner and Peterson's (1987) hypothesis is correct, amphetamine administration might be expected to lead to NE-related increases in response speeds and associated reductions in accuracy. That is, amphetamine administration might simply cause subjects to trade accuracy for speed.

Further evidence that supports the hypotheses that NE acts at relatively early stages of information processing has been reported by Sawguchi (1987a,b) who observed that iontophoretically applied NE tended to influence task-related firing in those premotor-cortical neurons active during the warning intervals of visual reaction time tasks. In contrast, DA tended to modulate the activities of prefrontal neurons active during the "go" phase of visual reaction time tasks (Sawguchi, 1987a,b). Some units responsive to NE in visual reaction time tasks had clearly defined visual receptive fields whereas others did not, an observation that led Sawguchi to suggest that those cells with receptive fields may function in visual-perceptual processes whereas those without receptive fields may function in attentional processes (Sawguchi 1987a,b).

In contrast, of the DA-sensitive units whose activities Sawguchi recorded, some had firing patterns coupled to the visual stimulus, some had firing patterns coupled to the motor response, and some had firing patterns coupled to the both stimulus and response. The effects of DA were strongest on units with firing patterns coupled to both stimulus and response, which led Sawguchi to suggest that prefrontal DA may primarily enhance activity involved in the association of perceptual information with motor responses (Sawguchi, 1987a,b; cf. Clark et al., 1987a; Oades, 1985). Of note, Sawguchi observed that NE reduced the response latencies of warning-phase responses by an average of approximately 44 ms; DA shortened the response latencies of "go" phase neurons by an average of 55 ms.

A number of other observations suggest that dopaminergic systems play roles in attention and reward processes. These include reports that damage to dopaminergic pathways can produce sensory neglect (Ljungberg & Ungerstedt, 1976), that dopaminergic blockers sometimes alleviate schizophrenic symptoms whereas dopaminergic agonists sometimes potentiate schizophrenic symptoms (schizophrenia is frequently characterized as an attentional disorder; Carlsson & Lindqvist, 1963; Davis, 1974), and by the body of evidence suggesting that dopaminergic activation is in some way associated with the rewarding properties of electrical brain stimulation. (The connection between reward and attentional processes derives from the notion that animals select and persist in those activities associated with reward, and that selecting and persisting in an activity amounts to attending to that activity.) For example, animals will work for electrical stimulation of the substantia nigra and the ventral tegmental area, the origins of two major systems of ascending dopaminergic projections (Routtenberg & Marlsbury, 1969; Crow, 1972). Furthermore, electrical stimulation of many of these structures' target areas, such as caudate nucleus, nucleus accumbens, septum, and prefrontal cortex, is rewarding (Olds, 1977).[5] Several investigations have shown that amphetamines enhance the effects of rewarding brain stimulation (Poschel & Ninteman, 1966; Stein & Ray, 1960). Because amphetamine is a potent dopamine

[5]Action-potential collision and conduction-velocity studies suggest that the neurons of the medial forebrain bundle (MFB) usually activated in self-stimulation experiments may actually conduct *downward* at relatively high velocities. In contrast, the dopaminergic axons of this pathway conduct upward at relatively low velocities. This suggests that dopaminergic neurons may not comprise the first stage of self-stimulation reward (Stellar, 1990). Nevertheless, much evidence suggests that dopamine does play a role in self-stimulation reward. For example, dopamine antagonists in the nucleus accumbens (recipient of a strong dopaminergic projection) reduce the effectiveness of MFB stimulation independent of motor effects (Stellar & Corbett, 1989), amphetamine or apomorphine in nucleus accumbens increases the effectiveness of MFB stimulation (Colle & Wise, 1986; Spencer & Stellar, 1986), and dopamine is released in nucleus accumbens during self stimulation (Blaha, Phillips, & Fibiger, 1988; Hunter, Hernandez, & Hoebel, 1988).

agonist, these observations are consistent with the notion that reward processes are at least modulated by dopamine mechanisms.

Performance effects of amphetamine-like drugs

The empirical data regarding the performance effects of amphetamine-like drugs are somewhat conflicting. Some reports indicate that these drugs improve vigilance; others indicate no such effects. Some studies have found memory improvements, other studies have found impairments, and some studies have found no effect. Some studies have shown that amphetamines affect motor processes and not decision processes; others have shown the opposite. Some studies have found that amphetamines affect specific tasks and not others; other studies of the same tasks have yielded conflicting results. These contradictions have been attributed to research-design flaws, such as low experimental power, ceiling effects, carry-over effects, inadequate subject training, and inattention to speed-accuracy trading (Fitzpatrick, Klorman, Brumaghim, & Keevover, 1988; Hockey, 1986). Other logical possibilities are that the drugs' performance-enhancing effects are, in fact, small and labile, or that they have performance-depressing side effects sufficient to counteract their performance-enhancing properties. These issues are reviewed in the following paragraphs.

Evidence that amphetamines may sometimes improve human performance includes reports of improved scores in pursuit tracking (Truijens, Trumbo, & Wagenaar, 1976), improved visual-scanning performance (Mohs, Tinklenberg, Roth, & Kopell, 1978), and reversal of sleep deprivation effects on vigilance and aircraft-instrument monitoring (Collins, 1977; Hartmann, Orzack, & Branconnier, 1977). Somewhat less clear evidence has been reported by Newhouse, Belenky, Thomas, Thorne, Sing & Fertig (1989), who recently reported that *d*-amphetamine improved performance in serial arithmetic and grammatical reasoning tests after sleep loss but did not improve performance on several other tests. The improvement in grammatical reasoning occurred after a postadministration delay of approximately 7 h. In contrast, Shappell, Neri, and DeJohn (1992), who used essentially the same tests, obtained no effect of methamphetamine on serial arithmetic and no effect on logical reasoning in moderately fatigued subjects. Shappell et al. (1992) did, however, observe trends toward improved performance on two spatial processing tests.

Methylphenidate-related improvements in memory search performance have been reported by Brumaghin, Klorman, Strauss, Lewine & Goldstein (1987) and by Peloquin & Klorman (1986). A later study performed in the same laboratory, however, yielded no such effect (Fitzpatrick, Klorman, Brumaghim & Keefover, 1988). A study by Babkoff et al. (1992), yielded no beneficial effects of methylphenidate on performance during sleep deprivation. Frowein (1988) reported data indicating that the amphetamine, phentermine, speeds motor responses but not decision times. In contrast, Halliday, Callaway, Naylor, Gratzinger, and Prael (1986) drew precisely the opposite conclusion for both methylphenidate and *d*-amphetamine. Perhaps the most widely-accepted result is that of Mackworth (1965), who reported that amphetamine improves vigilance performance. An attempt at replication by Coons et al. (1981), however, yielded no such effect.

In a comparison of amphetamine and barbiturate effects in humans, Frowein (1981) found that amphetamine shortened response-movement times without significantly affecting reaction times. This result was taken as suggesting that amphetamines influence response-system mechanisms and not perceptual and decision mechanisms. The magnitude of this effect varied as a function of stimulus-response compatibility, a result that also suggests that amphetamine might influence response-related processes. In contrast, a barbiturate lengthened reaction times without increasing response-movement times, suggesting that the drug may have had a site of action preceding the response system. The barbiturate effect was independent of stimulus-response compatibility and varied in magnitude with stimulus signal-to-noise ratio. This combination of effects suggests that the drug may have affected stimulus evaluation processes, rather than response processes. In apparent contrast, Frowein, Reitsma, and Aquarius (1981) reported amphetamine-related reductions in reaction time accompanied by

reductions in errors. This combination of effects (shortened response times and reduced errors) is consistent with a true increase in perceptual-decision efficiency but inconsistent with an explanation based on a simple increase in response speed. In light of the overall inconsistency of the experimental results on amphetamine, however, the generality of this result seems questionable (Hockey, 1986).

An explanation sometimes offered for the inconsistencies in the results on amphetamine effects is that the degree to which amphetamines affect performance might depend on fatigue level. Some authors have suggested that amphetamines may only reliably improve the performance of fatigued subjects (Frowein, Reitsma, and Aquarius, 1981; Weiss and Laties, 1962). It seems unlikely that this is the entire explanation, however, inasmuch as the data from fatigued subjects, reviewed above, are not greatly more consistent than those from nonfatigued subjects.

Amphetamines have been reported to improve memory in a number of studies involving nonhuman subjects (e.g., M'Harzi, Willig, Costa, & Delacour, 1988; Packard & White, 1989; Quartermain & Judge, 1983; Quartermain & Jung, 1989; Sara & Deweer, 1982; Strupp, Bunsey, Levitsky, & Kesler, 1991). In contrast, Ljungberg and Enquist (1987) have reported observing amphetamine-induced disruption of learned action sequences in rats that, nevertheless, were able to perform the separate behaviors comprising the sequences. These authors concluded that, contrary to studies that have employed simple tasks in which motor output is directly related to measures of performance, amphetamines do not increase performance in an adaptive way in more complex tasks.

An amphetamine-related disruption of human memory has been reported by Mewaldt and Ghoneim (1979), who found that, in delayed free recall, methamphetamine produced small increases in the probabilities with which subjects correctly recalled words from study lists and large increases in the probabilities with which subjects recalled words that *had not* been in the study lists. Mewaldt and Ghoneim suggested that the drug may have induced subjects to adopt less conservative retrieval criteria, thus causing them to generate more answers, most of which were incorrect. This result appears to differ from the effect of amphetamines on recognition performance (such as in memory search, discussed previously), which has usually been a slight improvement in performance or no effect at all. Logically, the mechanisms of recognition and recall differ at least in those operations responsible for converting the output of the memory system into task performance (Tulving, 1982). Thus, it seems entirely possible that amphetamines could influence recall without greatly affecting recognition via effects on output mechanisms. Data on the effects of amphetamines on recall performance are quite sparse. So, the phenomenon reported by Mewaldt and Ghoneim warrants further investigation.

Effects of amphetamines on response biases and perseveration

An important unanswered question regarding the effects of amphetamines on performance concerns whether the increased response speeds sometimes observed following their administration are attributable to increased efficiency or are results of changes in response biases that lead to overconfident or impulsive responding. The answer to this question is of substantial practical interest because a bias shift not offset by increased performance efficiency might seriously impair task performance. The degree to which amphetamines induce these effects in humans is unclear because investigators have rarely attempted to measure the effects of amphetamines on this type of response bias, despite the fact that such effects are readily mistaken for changes in efficiency in many widely used laboratory performance tests (Hockey, 1986). In particular, many investigators have inferred changes in efficiency from changes in reaction time without ruling out speed-accuracy trading as an explanation, despite the fact that an impulsive criterion shift with no change in efficiency can yield the same effect on reaction time as an increase in efficiency with no change in criterion. Response-bias shifts could occur, for example, as consequences of motor hyperactivity of the type accompanying direct activation of striatal dopaminergic neurotransmission (Kokkinidis and Anisman, 1976), or as consequences of an NE-mediated arousal process of the type hypothesized by Posner and Peterson (1990).

A study by Mewaldt and Ghoneim (1979) in which methamphetamine induced apparent shifts of decision criteria in free recall was discussed in the immediately preceding section. A few studies performed in nonhumans have used signal detection techniques in attempts to measure effects of amphetamines on response biases. Odor sensitivity, for example, is reportedly enhanced by low doses of amphetamine, whereas moderate doses depress sensitivity and alter response criteria (Doty & Ferguson-Segall, 1987). Amphetamine-induced lever biases, attributed to drug-induced perseveration, have been observed to degrade visual discrimination and attentional performance (Koek & Slangen, 1984; Ridley, Baker, & Weight, 1980; Sahgal, 1988). Andrews and Sahgal (1984) have reported, however, that amphetamine-related perseveration can occur in the absence of statistically reliable changes in signal-detection statistics, a result that might occur if the perseverated response were to vary from time to time. A further point to note is that amphetamine-induced perseveration may interact with stressor effects. For example, Anisman, Hahn, Hoffman, & Zacharko (1985) have reported that perseveration is enhanced by uncontrollable shock. Thus, experimental results could underestimate the magnitudes of interactions between amphetamine effects and operational stressor effects.

Summary of research on amphetamine-like drugs

The behavioral data indicate that amphetamines sometimes shorten response times. However, the data are equivocal about whether reductions in response times are accompanied by increased, decreased, or unchanged accuracy levels. This may be partly due to experimental design factors, particularly the scarcity of studies in which error rates have been measured precisely enough to determine whether amphetamine-related reductions in response times indicate impulsive responding, improved stimulus processing, or some mixture of the two (cf. Hockey, 1986). The neural studies considered here seem consistent with the idea that amphetamine may shorten behavioral response times by causing reductions in the response latencies of NE-sensitive neurons, DA-sensitive neurons or both (Sawguchi, 1987a,b). Amphetamine-related improvements in discrimination and recognition performance might be associated with the observed increases in the signal-to-noise ratios of sensory neuron discharge patterns (Foote et al., 1975; Kasamatsu & Heggelund, 1982; Videen et al., 1984; Waterhouse & Woodward, 1980). However, the increases in neural signal-to-noise ratios do not, in themselves, imply that amphetamines increase perceptual efficiency.

Whether conditions exist under which the dopaminergic effects of amphetamines enhance the ability to switch attention seems less clear, particularly given the tendency for high levels of DA to cause perseveration (Oades, 1985). If DA plays a role in facilitating the switching of attention (Clark et al., 1987a,b; Oades, 1985), one would expect an increase in DA to facilitate those types of behaviors that depend on shifts of attention, such as nonparallel multitasking and visual search. However, a recent behavioral study performed in humans suggests that dopamine depletion slows the process of responding to targets in cued locations in visual search tasks, without comparably slowing the ability to disengage attention from locations that do not contain targets (Clark, Geffen, & Geffen 1989). This result is consistent with the hypothesis that DA strengthens sensory-motor associations, but it is not obviously consistent with the hypothesis that DA facilitates switching.

The tendency for dopamine agonists, such as amphetamine, to induce response perseveration presents difficulties for the hypothesis that dopamine enhances attention switching (Oades, 1985). Oades suggests that perseveration at high DA concentrations might be accounted for by neural autoinhibition. A simple alternative explanation is that DA increases the strengths of stimulus-response associations (Sawguchi, 1987a). This hypothesis is consistent with the self-stimulation data (discussed previously), the tendency for amphetamines to cause perseveration, and the results of the Clark et al. (1989) visual-search experiments.[6] As previously discussed, amphetamine-induced perseveration is readily measured in nonhumans at fairly high doses. The

[6]The idea that DA mechanisms strengthen stimulus-response associations is, however, consistent with the idea that these mechanisms play a mediating role in attention switching. Thus, dopaminergic neurons might function under the control of other neural systems to modulate the strengths of stimulus-response associations.

degree to which it occurs in humans at customary doses does not appear to have been measured in a controlled experiment. Because detection-theoretic bias statistics are not necessarily sensitive to amphetamine-induced perseveration (Andrews and Sahgal, 1984), it might be necessary to obtain measures of sequential response dependencies to observe these effects.

EXPERIMENTAL HYPOTHESES

The ability of methamphetamine at 10 mg/70 kg to reduce SUSOPS deficits of vigilance and attention was examined by contrasting the performance of sleep-deprived subjects on a high-event-rate vigilance task (running short-term recognition memory) and a two-dimensional compensatory tracking task, both of which will be described presently. The measurements of primary interest were obtained after the stimulant and placebo had been administered during a period of sleep loss, in a sustained-work protocol. The conceptual null hypotheses of primary interest asserted that deficits in these tasks attributable to sustained performance would be unaffected by methamphetamine. The degree to which amphetamines at standard doses affect response criteria is unclear partly because experimental protocols that have been used to study their effects have frequently confounded changes in efficiency with effects of altered response criteria. The study described here addressed this issue by using highly practiced subjects and a large number of observations per subject, so that the accuracy measures might be reliable enough to detect changes in efficiency attributable to speed-accuracy trading.

A high-event-rate vigilance task (running recognition-memory) task was selected for use. The analyses of response-criterion effects presented in subsequent sections are based on measurements obtained in this task. The choice of the running-memory task was substantially motivated by Parasuraman's (1984) analysis of vigilance tasks. According to this analysis, high memory loads and high event rates are important factors in determining the degree to which sensitivity (as measured, for example, by d') will decline when attention must be sustained for long periods. The running-memory task imposes a high working-memory load, particularly when performed at high event rates. The task is a variant of the Continuous Performance Task (CPT; Orzack & Kornetsky, 1966; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). It might be noted that Williams et al. (1959) made effective use of the CPT in their seminal analyses of the performance of sleep-deprived subjects on experimenter-paced tasks.

A tracking task was also selected for this study, in order to obtain data of clear relevance to the psychomotor demands of flight and to help determine whether conclusions drawn from the vigilance data about the effects of methamphetamine on the effects of sustained performance might be peculiar to that task (which has a somewhat rhythmic, discrete-trials structure and a relatively heavy working-memory load). The tracking task required subjects to use a joystick to control the position of a moving cursor. Apart from the need to learn a set of relatively simple (first-order) system dynamics involved in using the joystick to control the cursor, the tracking task was not obviously demanding of memory. As in the case of the vigilance task, the conceptual null hypothesis asserted that deficits attributable to sustained performance (evidenced, in this case, by increases in overall tracking error) would be unaffected by methamphetamine.

METHODS

SUBJECTS

Subjects were 13 male naval and Marine aviation candidates stationed at Pensacola Naval Air Station. Their ages were 22-27 years (M = 24.00, SD = 2.00). The subjects' heights were 173-191 cm (M = 180.14, SD = 5.64). Their weights were 64-89 kg (M = 77.22, SD = 8.48). All subjects had normal or corrected-to-normal vision. All were medically screened before and after their participation.

EXPERIMENTAL TASKS

High event-rate vigilance (running memory). In the vigilance task, subjects were asked to monitor a randomly ordered sequence of upper-case letters, "A" through "Z," presented one at a time in the center of the computer monitor. The letters were displayed for 50 ms in white on a black background and measured approximately 5.5-mm high by 3.0-mm wide. Interstimulus intervals were 1250 ms measured from stimulus onset to stimulus onset. The letters were presented in the center of an 11.0-mm high by 9.5-mm wide box (inside dimensions) that served as an eye-fixation aid. The box was drawn in the center of the computer screen with vertical white lines 1-mm wide and horizontal white lines 0.5-mm wide. The fixation box was displayed continuously during each block of trials. A total of 480 stimuli were presented in each 10-min trial block.

Subjects were asked to decide whether or not each letter matched the letter immediately preceding it in the sequence. A random 50% of all letters matched the letter one position back in the sequence. Subjects responded by pressing a response key with the first finger of one hand whenever a letter matched its immediate predecessor and another key with the first finger of the opposite hand when a letter differed from its immediate predecessor. Matching stimuli were referred to as "targets"; nonmatching stimuli were referred to as "nontargets." The two response keys were "F" and "J." The assignment of dominant and nondominant hands to target and nontarget response keys was counterbalanced across subjects.

Two-dimensional compensatory tracking task. In the tracking task, subjects used a joystick to compensate for random direction changes in a continuously moving cursor displayed on the computer screen. The subject's task was to keep the cursor's X-Y position centered on a set of crosshairs in the middle of the screen. System dynamics were first-order (velocity) on both X and Y coordinates. The dependent measure was the root-mean-squared (RMS) error of the cursor's position measured relative to the crosshairs (i.e., the cursor's time-averaged Euclidean distance from the crosshairs). The duration of each tracking session was 10 min.

Sleep-quality questionnaire. Following a period of postexperimental recovery sleep, subjects were asked to fill out a brief sleep-quality questionnaire. The questionnaire asked subjects to judge how much trouble they had encountered in falling asleep, how long it had taken them to fall asleep, how many times they recalled waking up, how rested they felt upon awakening, whether they felt they needed more sleep, their mood upon awakening, and the number of dreams they recalled.

PROCEDURE

Subjects were run in subgroups of three-six individuals and monitored continuously by project staff. Each subject was comfortably seated approximately 1 m from a desktop computer that presented stimuli and collected the subject's responses. A training session was held on each of the four mornings preceding the sustained-performance session. Each task was practiced twice in each session, for a total of 3840 trials in the running-memory task and 80 min in the tracking task. The sustained-performance session was 13.5 h in duration. It began at 1930 hours in the evening of the last practice day and ended at 0900 the next morning. Subjects were asked to carry out a normal day's activities and to refrain from napping before reporting to the laboratory for the sustained-performance session.

The sustained-performance session consisted of nine "superblocks" of experimental tasks spaced 90 min apart. Each superblock consisted of three experimental tasks and a sleepiness scale.[7] The tasks in each

[7]A memory-search task was used in a substudy of the effects of fatigue and methamphetamine on controlled and automatic processing. For clarity and balance, the automaticity study is described in a companion report (Stanny, McCardie, & Neri, In press). The results and conclusions of that study extend those described here;

superblock were separated by breaks of approximately 5 min. Electrocardiograms were monitored telemetrically throughout the sustained-performance session. Measurements of vital signs (heart rate, blood pressure, and oral temperature) were recorded after each superblock at the beginning of a 20-min break. Food and noncaffeinated drinks were available during the breaks between superblocks. At 0116, seven, randomly selected subjects received a capsule containing 10 mg/70 kg body weight of dextromethamphetamine hydrochloride. The remaining subjects received identical capsules containing cornstarch. Standard double-blind procedures were followed. After the main session, subjects had breakfast, showered, and slept in the laboratory dormitory for at least 6 h, or for as long as they desired. After waking, subjects completed the sleep-quality questionnaire, were interviewed by a physician, and released to go home.

DATA ANALYSES

Vigilance performance. In the vigilance task, reaction times were measured from stimulus onset to response onset. Responses with reaction times less than or equal to 100 ms were considered anticipation errors (fast guesses) and were analyzed separately from other responses. The reaction times of correct and incorrect responses that were not fast guesses were measured from stimulus onset to response onset. Trials on which a subject did not respond were counted as nonresponses. Nonresponses, like fast guesses, were analyzed separately from other types of responses.

Accuracy was measured in units of the detection-theoretic sensitivity index, d' (Green & Swets, 1966). The value of d' was calculated as $d' = \Phi^{-1}[p(H)] - \Phi^{-1}[p(FA)]$, where $\Phi^{-1}[p(H)]$ is the inverse cumulative normal probability function evaluated at the subject's hit rate, $p(H)$, and $\Phi^{-1}[p(FA)]$ is the same function evaluated at the subject's false-alarm rate, $p(H)$. The value of $p(H)$ was estimated as the number of target-present trials on which the subject responded "target present" divided by the number of target-present trials on which the subject responded either "target present" or "target absent." That is, the hit rate was taken as the number of correct "target present" responses divided by the number of target-present trials that yielded neither a fast guess nor a nonresponse. The value of $p(FA)$ was estimated as the proportion of all target-absent trials on which the subject responded "target present" divided by the number of nontarget trials on which the subject responded either "target present" or "target absent." That is, the false-alarm rate was taken as the number of incorrect "target present" responses divided by the number of nontarget trials that yielded neither a fast guess nor a nonresponse.

At various points in the text, relative sensitivities are expressed as efficiencies. Efficiency was calculated as the ratio of an obtained value of d' and a reference sensitivity and expressed as a percentage. The reference sensitivity was the value of d' achieved at the beginning of the sustained-performance session (at 1930). (Statistical analyses relevant to performance efficiency, however, were performed using the original values of d'.) The value of efficiency thus obtained was equal to 100 times the square-root of the efficiency measure of Signal Detection Theory, $\eta = (d'_{obt} / d'_{ref})^2$, where d'_{obt} is an obtained sensitivity and d'_{ref} is a reference sensitivity (Green & Swets, 1966). Efficiency was taken as proportional to $\eta^{1/2}$, for our purposes, because squaring the ratio of obtained and reference d' values has no clear rationale in the present application.[8]

The detection-theoretic measure of response bias, the log likelihood ratio ($\log(\beta)$; Green & Swets, 1966; Macmillan & Creelman, 1990), was also derived from hit and false-alarm probabilities calculated as

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they in no way qualify the results and conclusions presented here.

[8]The sensitivity measure d' is voltage-like in that its unit of measure is a root-mean-squared noise amplitude, σ_{Noise}. Squares of d' ratios, therefore, have properties similar to mean-squared power ratios, which are conventional measures in the electrical and acoustical settings in which η has most frequently been used.

previously described. The value of log(β) indicates the degree to which a subject is biased toward making one or another of the available responses, "target present" and "target absent" in the case at hand. Positive values of log(β) indicate a preference for responding "target absent"; negative values indicate a preference for responding "target present"; a value of 0.0 indicates unbiased responding.[9] Under standard Signal Detection Theory assumptions, log(β) is the natural logarithm of the ratio of ordinates of the distributions of internal representations of target and nontarget stimuli on the subject's decision axis, at the point of the subject's response criterion. The calculating formula was $\log(\beta) = -.5[\Phi^{-1}(p(H)) + \Phi^{-1}(p(F))] / [\Phi^{-1}(p(H)) - \Phi^{-1}(p(F))]$, in which the symbols on the right of the equality are defined as in the preceding paragraphs.

Compensatory Tracking. Tracking performance was measured as the root-mean-squared (RMS) distance in pixels between the location of the moving cursor and the crosshairs drawn in the center of the screen. That is, the RMS error measurement was the time-averaged Euclidean distance, angle ignored, between cursor and crosshairs. Subjects were allowed the first minute of each 10-min tracking session to center the cursor and settle into the task. The data from the initial minute were ignored. The summary RMS measure for each tracking session was calculated by averaging the data obtained in minutes 2-10.

SIGNIFICANCE TESTS

Significance tests were performed in mixed, within- and between-subjects, factorial analyses of variance (ANOVAs). The calculations were performed with BMDP 2V (Dixon, Brown, Engelman, Hill, & Jennrich, 1988). The drug manipulation formed a between-subjects factor that applied to the analysis of each dependent measure. It had two levels corresponding to the methamphetamine and placebo treatment groups. The vigilance task yielded four dependent measures, reaction time, nonresponse probability, sensitivity (d'), and bias (log(β)). These were analyzed in separate ANOVAs. The primary analysis of the running-memory reaction times was a 2 × 2 × 2 × 9 factorial design with one between-subjects factor and three within-subject factors. The between-subject factor was treatment group; the within-subject factors were stimulus type (target and nontarget), response correctness (correct or not), and time (trial blocks 1 through 9). The analysis of nonresponses was like the analysis of reaction times except that it contained no correctness factor. The analyses of d' and log(β) were like the analysis of nonresponses except that they contained no stimulus-type factor (because correctness and stimulus types both disappear in the calculations of d' and log(β)). The tracking task had one dependent measure, RMS tracking error. It was analyzed in a 2 × 9, groups by time, mixed ANOVA. Similarly, systolic and diastolic blood pressure, oral temperature, and heart rate each had one dependent measure. These too were analyzed in 2 × 9, treatment-group by time, mixed-factorial ANOVAs.

The major a priori hypotheses concerned differences between trends in the groups' performance over time. Except where otherwise noted, differences between the groups' performance trends in time were examined by deriving linear orthogonal-polynomial contrasts for a dependent measure over the nine task blocks and then contrasting the trends between the two groups. The orthogonal-polynomial contrasts have one numerator degree of freedom (*df*) and do not require correction for covariance-matrix nonsphericity and the resulting inflation of *F* ratios encountered in repeated measures ANOVAs with more than one numerator *df* (Dixon et al., 1988). Wherever a significance level is reported for a repeated measures *F* ratio with more than one numerator *df*, the reported value of *p* is the value obtained after correcting for nonsphericity effects by the procedure of Huynh and Feldt (1976).

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[9]To avoid a possible confusion, note that values of log(β) do not directly reflect "biases" of the type that lead subjects to respond quickly and inaccurately versus slowly and cautiously. Thus, an amphetamine-related "criterion shift" that leads to impulsive responding would not necessarily influence log(β).

RESULTS AND DISCUSSION

Average vigilance sensitivities (values of *d'*) declined systematically in both groups prior to drug administration and for at least the first half-hour postadministration (see Figure 1). By 0153 hours, some 37 min postadministration, efficiency (the ratio of current and initial *d'* values multiplied by 100%) had declined to 70% in the placebo group and 67% in the methamphetamine group. At 2+7 (2 h 7 min) postadministration, however, efficiency returned to 89% in the methamphetamine group and averaged 87% until the final measurement was taken at 0753. In contrast, efficiency continued to decline during the postadministration hours in the placebo, reaching 60% at 2+7 postadministration and averaging only 46% during the circadian nadir between 0453 and 0753. During the nadir, the methamphetamine group performed with an average efficiency equal to fully 187% of the efficiency of the placebo group. The overall declining trend in *d'* over time, conservatively averaged across both treatment groups, yielded a highly significant $F(1, 11) = 31.47$, $p = .0002$. The difference between the performance trends in the methamphetamine and placebo groups yielded a value of $F(1, 11) = 19.6$, $p = .0010$.

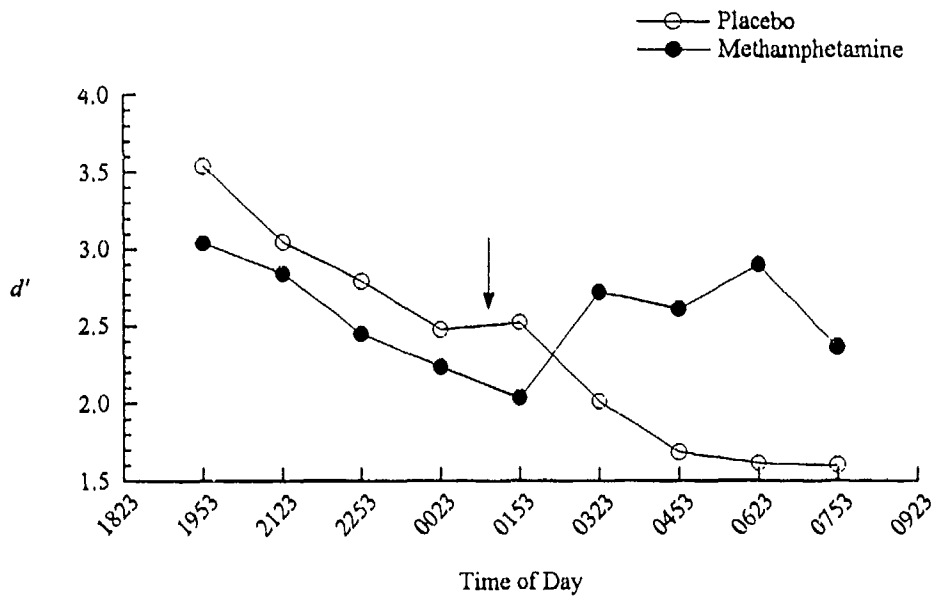

Figure 1. *Mean sensitivity (d') versus time in the vigilance task. The arrow indicates drug administration.*

The response-bias measure, log(β), averaged 0.20 over groups and trial blocks. This value significantly exceeded 0.0, $F(1, 11) = 9.79$, $p = .0096$, indicating the presence of a small conservative bias in favor of responding "target absent." Subjects' responding appeared to become somewhat more liberal (or more neutral) over time, declining from an initial log(β) = 0.33 at 1953 to an average log(β) = 0.18 at 0753. However, this apparent trend was nonsignificant. A similar, nonsignificant trend toward increasingly liberal responding was observed in one task in the sleep-deprivation experiment of Newhouse et al. (1992). In that experiment, a 20-mg dose of *d*-amphetamine, furthermore, produced a significant conservative shift in bias. The 10 mg/70 kg dose of *d*-methamphetamine used in the present experiment, however, did not produce compelling evidence of a bias shift (that is, time-course of log(β) did not vary significantly between groups).

Correct-response reaction times (Figure 2) increased by an average of 43.8 ms during the night, from an overall mean of 412.0 ms at 1953 to an overall mean of 455.8 ms at 0453 and 0623. Correct response times then declined slightly to 449.1 ms at 0753 in the final block of trials. The linear component of the increase in RT over time was significant, producing a value of $F(1, 11) = 8.08$, $p = .0160$. The linear trend did not differ significantly between methamphetamine and placebo groups. However, an examination of Figure 2

suggests that methamphetamine-group reaction times increased more rapidly than placebo-group reaction times before 0153, and then decreased substantially (by 52 ms) in the 0323 block of trials (2+7 postadministration). This pattern in the methamphetamine group's correct-response reaction times suggests that the stimulant may have counteracted a comparatively rapid increase in methamphetamine-group reaction times. The presence of a difference in the second-order components of the groups' trends in correct-response reaction time over time suggests that this interpretation might be correct, $F(1, 11) = 4.88$, $p = .0493$. Correct responses to on target-present trials averaged 48.1 ms faster than correct responses target-absent trials, $F(1, 11) = 54.75$, $p < .00005$, a standard effect in matching designs (Luce, 1986). The difference between target-present and target-absent reaction times did not change significantly over time. The difference between target-present and target-absent reaction times was not affected by the drug treatment.

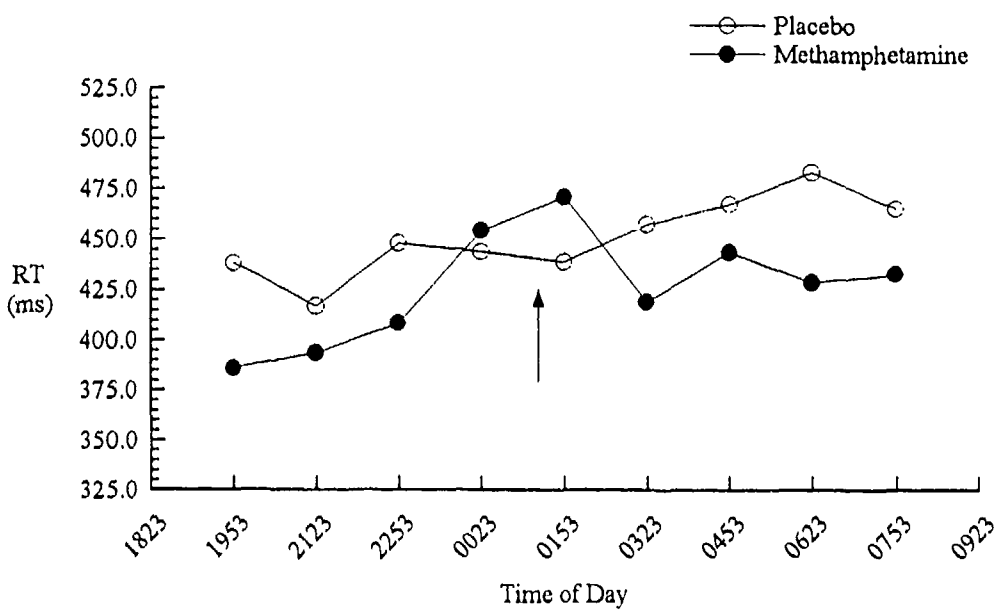

Figure 2. *Mean correct-response reaction times (RTs) versus time in the vigilance task. The RTs have been averaged across target-present and target-absent trials. The arrow indicates drug administration.*

On average, incorrect-response reaction times were shorter than correct-response reaction times at the beginning of the run, averaging 400.1 ms versus 412.0 ms for correct responses in the first block of trials at 1953. Incorrect-response reaction times, however, increased more rapidly with time, reaching 458.9 ms versus 449.1 ms for correct responses in the final block of trials at 0753. The difference between the linear components of the trends in correct- and incorrect-response reaction times was significant, $F(1, 11) = 8.19$, $p = .0155$. Like correct-response reaction times, error reaction times decreased in the methamphetamine group between 0153 and 0323, by an overall average of 45 ms. In the error data, however, this phenomenon missed significance, yielding an $F(1, 11) = 3.75$, $p = .0789$ for the contrast of the second-order polynomial trend

Nonresponse probabilities from the two groups (estimated from the proportions of trials on which subjects did not respond) are shown in Figure 3. The overall probability of a nonresponse averaged across stimulus types and groups increased from essentially zero (0.001) in block 1 at 1953 to a maximum of 0.236 in

the seventh block at 0453. Nonresponses then decreased to a final value of 0.162 at 0753. The increasing trend in nonresponding over time was significant, $F(1, 11) = 19.81$, $p = .0010$.

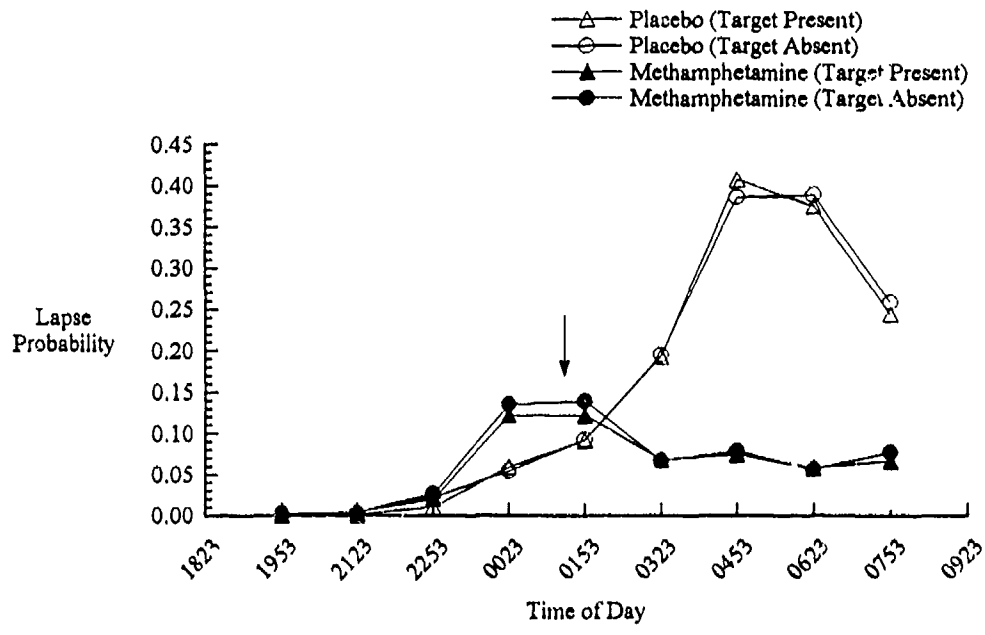

Figure 3. *Nonresponse (lapse) probabilities versus time in the vigilance task. The arrow indicates drug administration.*

Like reaction times, nonresponse probabilities at first increased more rapidly in the methamphetamine group than in the placebo group (Figure 3), reaching an overall average of 0.128 at 0023 in the methamphetamine group versus 0.057 at 0023 in the placebo group. By 0323 (2+7 postadministration), however, nonresponse probabilities had decreased to 0.068 in the methamphetamine group versus 0.194 in the placebo group. Nonresponse probabilities in the methamphetamine group subsequently averaged 0.068 through until the final block of trials at 0753, which was 6+37 postadministration. In contrast, nonresponding increased after 0153 in the placebo group, reaching a mean of 0.389 at 0453 and 0623, and then decreased to 0.251 in the final block of trials at 0753. The difference between the (linear) trends in nonresponse probabilities in methamphetamine and placebo groups yielded a highly significant $F(1, 11) = 10.42$, $p = .0080$.

An inspection of Figure 3 suggests that nonresponse probabilities did not differ between target-present and target-absent trials. Overall, the placebo group failed to respond on 15.4% of all target-present trials and on 15.6% of all target-absent trials. The methamphetamine group failed to respond on 6.0% of all target-present trials and on 6.5% of all target-absent trials. The slightly greater probability of a nonresponse on target-absent trials (0.4%, averaged across groups) was reliable enough to yield a modest trend toward significance, $F(1, 11) = 4.06$, $p = .0694$. It seems possible that, in forced-paced tasks of this type, such effects might be due to a slowing of responding that causes the reaction times of some responses to exceed the interstimulus interval. Trials on which this occurs are counted as nonresponses, although they may simply be trials on which responses occur after the deadline. As previously noted, the reaction times of correct target-absent responses in matching designs are systematically 40-50 ms longer than the reaction times of correct target-present responses. For this reason, one might expect more target-absent responses than target-present responses to have reaction

times longer than the interstimulus interval. Thus, one might expect forced-paced tasks to yield more (apparent) nonresponses on target-absent trials than on target-present trials.[10]

Fast guesses in the vigilance task (responses with reaction times of 100 ms or less) increased from an overall average of 0.08/block at 1953 to a maximum of 5.27/block in the final set of trials at 0753. The overall, increasing trend in fast guesses was significant, $F(1, 11) = 12.34$, $p = .0049$. Fast guesses increased more rapidly in the methamphetamine group than in the placebo group until 0153 (37 min postadministration) and then decreased somewhat. In contrast, fast guesses continued to increase until the final block of trials in the placebo group. The apparently beneficial impact of the methamphetamine treatment on fast guesses was not reflected by a significant difference in group trends. Nevertheless, the data provide no evidence to suggest the presence of a methamphetamine-related *increase* in fast-guess probabilities. If anything, the pattern of the means suggests the possibility that methamphetamine reduced fast guesses.

Figure 4 shows RMS tracking error versus time in the placebo and methamphetamine groups. The performance of the methamphetamine group was slightly superior to that of the placebo group prior to drug administration. Tracking error increased slightly in both groups during the hours prior to drug administration. Thereafter, the methamphetamine group's performance remained stable through the final tracking session at 0739 (6+23 postadministration). In contrast, tracking error in the placebo group increased markedly, reaching a maximum at 0323, and then declined somewhat through the final tracking sessions. The overall increasing trend in RMS error (averaged across methamphetamine and placebo groups) yielded a significant $F(1, 11) = 14.04$, $p = .0032$. The difference between the linear components of the trends in the methamphetamine and placebo groups' RMS error measurements was also significant, $F(1, 11) = 7.65$, $p = .0184$.

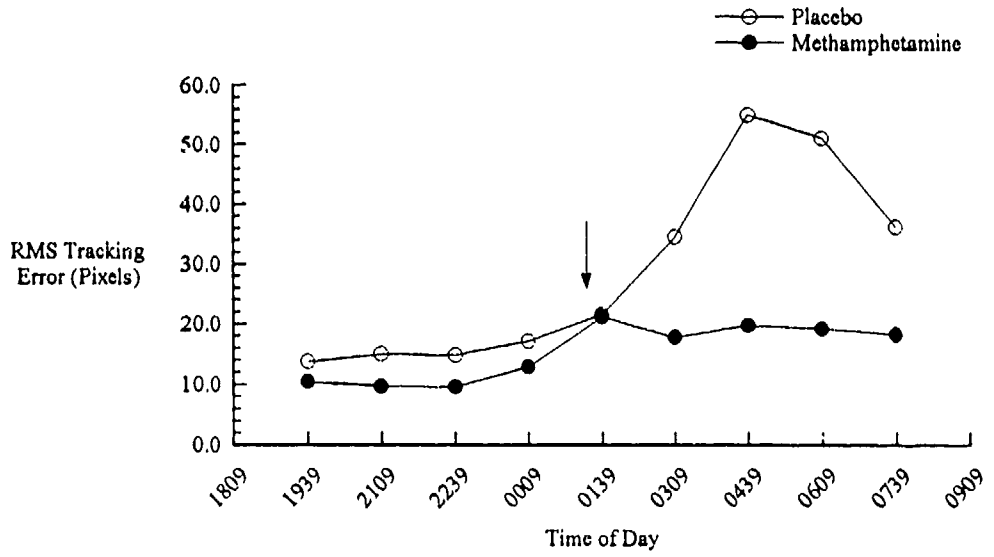

Figure 4. *Pursuit-tracking error versus time for the placebo and methamphetamine groups. The arrow indicates time of drug administration.*

[10]It might be noted that the widely used, ad hoc practice of treating responses with reaction times more than twice the rested mean reaction time as lapses (in data from subject-paced tasks) would be expected to yield a similar result.

The methamphetamine treatment yielded a substantial effect on the time-course of body temperature. Temperature in the placebo group declined systematically, reaching an apparent circadian minimum near the time of the 0538 measurement and rising slightly thereafter (Figure 5). In contrast, temperature in the methamphetamine group declined until drug administration but then increased sharply between the 0238 and 0408 measurements (0408 was 2+52 postadministration). Body temperature, thus, increased by an average of about 0.25 °C within 3 h of administration in the methamphetamine group, and by approximately 0.75 °C by the time of the final measurement at 0838. This pattern of effects yielded a significant difference in the groups' temperature trends over time, $F(1, 11) = 9.05$, $p = .0119$.

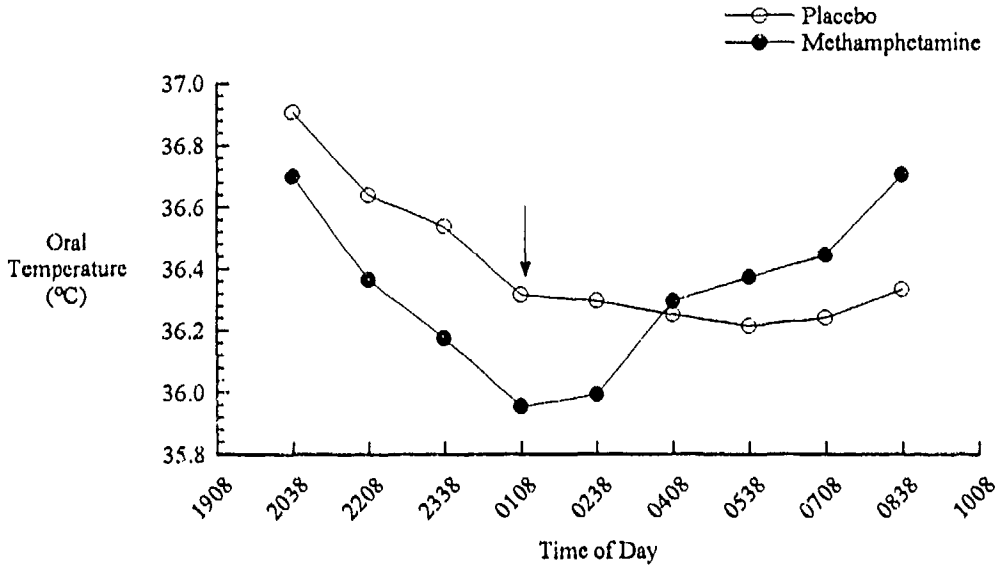

Figure 5. *Body temperature versus time. The arrow indicates drug administration.*

Heart rate did not vary significantly as a function of the drug treatment. Average systolic blood-pressure measurements obtained from the methamphetamine group increased from a range of 109-110 mm Hg prior to drug administration to a range of 120-124 mm Hg in the four final measurements (Figure 6). In contrast, systolic pressure remained approximately constant, or perhaps increased slightly, in the placebo group, averaging 115-120 mm Hg prior to administration and 120-123 mm Hg in the four final measurements. A similar pattern was observed in the diastolic measurements. There, the means from the methamphetamine group ranged from 66-77 mm Hg prior to drug administration and then increased to 78-81 mm Hg during the four final measurements. In contrast, the averaged diastolic measurements from the placebo group ranged from 78-83 mm Hg prior to administration and from 77-82 mm Hg after administration (Figure 6). A test of the difference between the linear components of the placebo and methamphetamine groups' blood-pressure measurements (averaged across the systolic and diastolic readings) yielded a trend toward significance, $F(1, 11) = 4.29$, $p = .0628$. The effect of methamphetamine did not differ between systolic and diastolic measurements.

An analysis of responses to the questions in the recovery-sleep quality questionnaire produced no significant differences between the methamphetamine and placebo groups. An examination of patterns in the subjects' responses, however, suggested the possible presence of a mild amphetamine-like effect on sleep. This

was suggested by observations that the methamphetamine subjects reported lying awake longer, on average, than placebo subjects, a mean of 16.2 min for methamphetamine subjects versus 9.0 min for placebo subjects, and that the methamphetamine subjects reported having fewer dreams than placebo subjects, an average of 0.29 for methamphetamine subjects versus 1.33 for placebo subjects. (The difference in reported sleep latency was attributable largely to one subject who reported lying awake for 45 min.) On the other hand, methamphetamine subjects reported waking up in slightly better moods and feeling slightly more rested than placebo subjects.

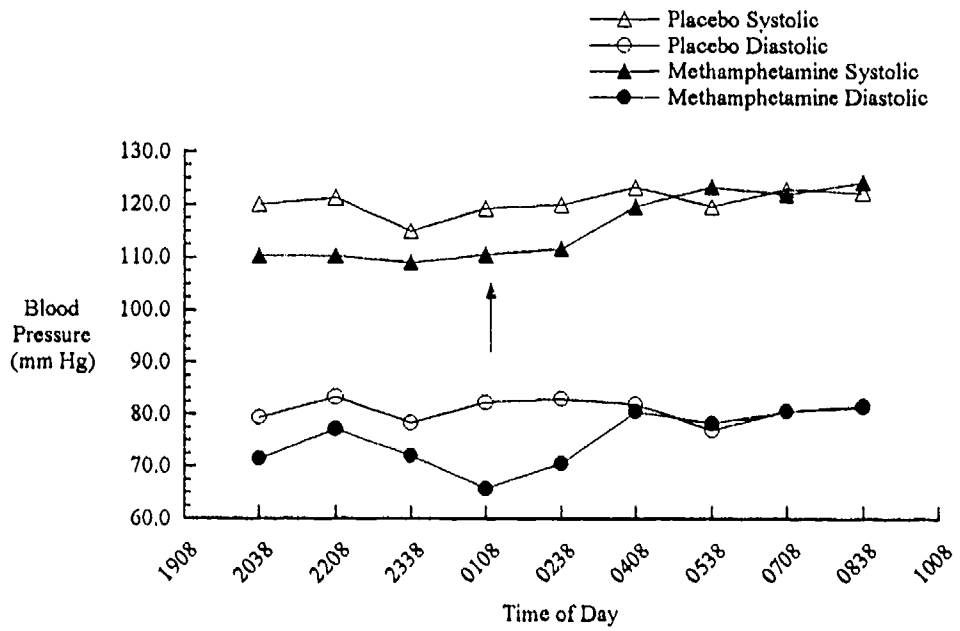

Figure 6. *Blood pressure versus time. Arrows indicate drug administration.*

GENERAL DISCUSSION

The 10 mg/70 kg methamphetamine treatment markedly reduced the effects of sustained performance on vigilance and tracking. After an initial preadministration decline, vigilance efficiency in the methamphetamine group returned to 87% of its initial level approximately 2+7 after administration. Efficiency in the methamphetamine group remained near that level until the end of the experiment 6+37 later. In contrast, vigilance in the placebo group declined to approximately 46% of its initial level during the hours of the early-morning circadian low (during the 0453 and 0753 trial blocks). Hence, *on non-lapse trials alone*, the vigilance efficiency of the methamphetamine group exceeded that of the placebo group by 89% during the hours from 0453 to 0753 (100% × (87%/46%) = 189%). Lapses were much less frequent in the methamphetamine group than in the placebo group during the night and early morning. Lapses occurring on approximately 7% of all trials in the methamphetamine group during the hours from 0453 to 0623. In contrast, lapses occurred on 39% of all trials in the placebo group during these hours.

The high level of vigilance efficiency displayed by the methamphetamine treatment group is inconsistent with predictions that the stimulant would merely induce faster, less careful responding. The hypothesis that the stimulant would affect performance by causing subjects to adopt more liberal response criteria, responding more rapidly but less accurately, yields predictions that (a) the methamphetamine treatment should produce reductions in reaction time, and (b) these reductions in reaction time should cause the methamphetamine treatment to yield reductions in *d'*. The uniformly *higher* values of *d'* obtained in the methamphetamine condition disconfirms this hypothesis. An ad hoc explanation for the higher accuracy observed in the methamphetamine condition, that methamphetamine caused subjects to become more cautious and trade reductions in speed for increases in accuracy, is inconsistent with the absence of evidence for a methamphetamine-related slowing of responding. Indeed, the analysis of reaction times from this experiment suggests that methamphetamine, in fact, counteracted an initial decline in response speed.

This result does not imply that methamphetamine had *no* influence on speed-accuracy trading. Logically, the methamphetamine treatment could have produced both an increase in vigilance and a shift toward less conservative responding. The present data indicate, however, that the increase in efficiency in the methamphetamine group was more than sufficient to compensate for any speed-accuracy trading that may have occurred: Subjects who received the drug may have been able to adopt less cautious response strategies and still outperform subjects who received the placebo. Contrary to this hypothesis, however, the analysis of fast guesses in the vigilance experiment disclosed no evidence to suggest that methamphetamine in any way tended to increase impulsive responding. In fact, the methamphetamine treatment was associated with a small (and nonsignificant) reduction in fast guesses. This observation lends further support to the idea that the dominant effect of the methamphetamine treatment was to increase vigilance efficiency.

The methamphetamine treatment substantially reduced the effects of sustained performance on tracking errors. Average control error in the methamphetamine group increased by 89%, relative to its 1930 level, during the early morning (at 0323). Although the increase in control error in the methamphetamine group was not trivial, it contrasts markedly with the 401% increase in control error observed in the placebo group over the same period. Because the task was fairly demanding and errors increased rapidly with inattention, even a brief lapse could result in a total loss of control and a "catastrophic" increase in error. Such events may account for the relatively large increases in tracking error that occurred in both groups during the early morning.

A possible drawback of using amphetamines to counter SUSOPs effects is that low and moderate doses have sometimes been observed to induce paradoxical drowsiness during the first hour post administration (Tecce & Cole, 1974). This observation might conceivably be related to reports that amphetamine, which at higher concentrations tends to increase norepinephrine release from the terminals of locus coeruleus projection neurons, sometimes *reduces* norepinephrine release at low doses (Huang & Maas, 1981; Ryan, Tepper, Young, & Groves, 1985). The frequency with which amphetamine-related paradoxical drowsiness occurs, and the conditions under which it occurs, are unclear. We observed no effects that would suggest such an effect occurred in this study.

Other issues surrounding the use of amphetamines in sustained or continuous operations derive from the well-known tendency for amphetamines to induce insomnia and change the electroencephalographic structure of sleep (Hart & Wallace, 1975; Hartmann & Cravens, 1976). Because amphetamines can interfere with sleep long after administration, despite previous sleep deprivation (Newhouse et al., 1989; Penetar et al., 1991), a more rapidly eliminated (or less insomnia producing) drug might be better suited to naval flight operations. Questions thus remain about the size of the sleep-latency increase to plan for when amphetamines have been administered during SUSOPS and the precise amount of additional recovery-sleep to plan for when amphetamines are used to counteract sleep loss. These issues warrant further study. A new antihypoarousal drug, modafinil, reportedly approaches the effectiveness of the amphetamines and produces neither significant insomnia nor other amphetamine side effects (Lagarde, 1990; Lagarde & Milhaud, 1990; Mitler & Hajdukovic, 1991; see Lyons & French, 1991, for a review). Modafinil will soon enter U.S. clinical trials as a treatment

for narcolepsy. If modafinil proves effective as an antifatigue agent, it may represent a safer alternative to the amphetamines.

A further set of issues concerns dose regimes. The most practical way to administer amphetamines under naval air combat conditions may be to issue small quantities to flight crews with advice such as (1) take the smallest effective dose upon becoming drowsy, (2) repeat the dose at appropriate intervals, and (3) continue taking the drug until the end of the mission, to avoid a letdown. Because amphetamines may interact with stressors (Anisman et al., 1985), the advice about dose timing might warrant modification to avoid a peak drug effect just before landing. Some important unknowns with respect to this advice include the most appropriate time intervals between doses, the number of consecutive doses that will be effective, whether and how doses should be varied with time, and the appropriate timing of doses with respect to major stressful mission events.

Little or no evidence bears on questions about minimal effective doses for use in sustained naval air operations. Past Air Force experience suggests that a nominal dose of 5 mg of *d*-amphetamine may protect against fatigue in combat settings with few side effects. Because Air Force pilots have been issued *d*-amphetamine in several 5-mg tablets and instructed to take the drug until it is effective (which might require more than one dose), the actual effective dose of *d*-amphetamine is unknown.[11] In contrast, Army laboratory data suggest that 20 mg of *d*-amphetamine may be needed to maintain performance (Newhouse et al., 1989; 1992). This result, obtained after 2 days of sleep deprivation, was accompanied by significant side effects. Because Navy pilots do not usually fly after 2 days of total sleep deprivation, and because major side effects render a drug unsuitable for carrier operations, a 20-mg dose of *d*-amphetamine is of questionable relevance to Navy flight operations. Our data suggest that 10-mg of *d*-methamphetamine may be adequate to ameliorate the effects of one night of sleep loss with few side effects. Whether a single 5-mg dose of *d*-amphetamine would yield comparable results is currently an open question.

It also is important to directly compare the effects of caffeine to those of the amphetamine-like drugs. If similar effects can be obtained with caffeine, there may be little reason to resort to controlled substances. Promising results from the Walter Reed Army Institute of Research suggest that a single, large dose of caffeine may yield effects on sleep deprivation comparable to those of a low dose of *d*-amphetamine. Recent data from the Naval Health Research Center, however, suggest that this result may hold only for a single caffeine dose administered after a significant period of abstinence (T. Kelly, Naval Health Research Center, Personal Communication, May, 1993). It will be important to clarify this issue.

CONCLUSIONS AND RECOMMENDATIONS

1. The methamphetamine treatment largely eliminated vigilance deficits in 13.5 h of sustained performance during a night of sleep deprivation. Nonresponses (lapses) were prevalent in the placebo group's performance during the early-morning hours. Lapses were much less frequent in the methamphetamine group during these hours. The drug's striking ability to reduce lapse-related vigilance deficits may be the strongest argument for its efficacy.

2. The methamphetamine treatment did not induce faster, less careful responding. This was evidenced by an overall, methamphetamine-related improvement in performance efficiency, and by the absence of methamphetamine-related increases in impulsive responding (fast guesses).

3. Tracking errors increased markedly in the placebo group during the night. The methamphetamine treatment substantially reduced these errors.

[11]It should be noted that current Air Force policy forbids the use of stimulants.

4. The methamphetamine treatment became maximally effective within approximately 2-3 h of administration. Its effects did not disappear entirely through the final rounds of testing, approximately 6-7 h postadministration.

5. The methamphetamine treatment yielded moderate increases in blood pressure that averaged near 10 mm Hg for both systolic and diastolic measurements.

6. Like the other amphetamines, methamphetamine increases body temperature. The average increase in the present study was estimated at approximately 0.75 °C. This suggests that amphetamines should be avoided when hyperthermia might pose a threat.

7. Although the 10 mg/70 kg dose of *d*-methamphetamine used in this study did not significantly affect reported sleep latencies, the pattern of subjects' sleep-quality reports resembled the known effects of amphetamines on sleep. Thus, it might be anticipated that methamphetamine may occasionally produce insomnia in some individuals as long as 6-7 hours postadministration, even following a night of sleep deprivation. It would be important to plan for this possibility were *d*-methamphetamine to be used in conditions that require personnel to sleep soon after the end of a mission.

8. It should be noted that amphetamines are not currently approved for use in naval air SUSOPs. A consideration of effectiveness of the amphetamines in countering fatigue, and the potential consequences of fatigue in air operations, suggests that this policy might warrant review.[12]

[12]It might be noted that *d*-amphetamine is currently approved for use in countering the memory and vigilance deficits caused by scopolamine-based treatments for airsickness.

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We examined the effects of a 10 mg/70 kg oral dose of *d*-methamphetamine HCl on high-event-rate vigilance and tracking performance in a 13.5-h sustained-performance session during a night of sleep loss. At 0116 hours, seven subjects were administered *d*-methamphetamine, double-blind. The remaining six subjects were given a placebo. Values of sensitivity (*d'*) in the vigilance task declined markedly during the night in the placebo group. The methamphetamine treatment reversed an initial decline in *d'* within approximately 2 h of administration. The methamphetamine treatment also reversed increases in nonresponses (lapses) within approximately 2 h of administration. Tracking performance also declined markedly during the night in the placebo group. The methamphetamine treatment reversed the decline in tracking performance. An analysis of fast guesses in the vigilance experiment disclosed no evidence to suggest that methamphetamine tended to increase impulsive responding. In fact, the methamphetamine treatment was associated with a small (and nonsignificant) reduction in fast guesses. The overall pattern of the results suggests that methamphetamine at 10 mg/70 kg produces genuine increases in efficiency that effectively counteract the effects of continuous work during a night of sleep loss.

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